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NEWS	2		"Ask CAS" for self-help around the clock
NEWS	3	SEP 01	New pricing for the Save Answers for SciFinder Wizard within STN Express with Discover!
NEWS	4	OCT 28	KOREAPAT now available on STN
NEWS	5	NOV 30	PHAR reloaded with additional data
NEWS	6	DEC 01	LISA now available on STN
NEWS	7	DEC 09	12 databases to be removed from STN on December 31, 2004
NEWS	8	DEC 15	MEDLINE update schedule for December 2004
NEWS	9	DEC 17	ELCOM reloaded; updating to resume; current-awareness alerts (SDIs) affected
NEWS	10	DEC 17	COMPUAB reloaded; updating to resume; current-awareness alerts (SDIs) affected
NEWS	11	DEC 17	SOLIDSTATE reloaded; updating to resume; current-awareness alerts (SDIs) affected
NEWS	12	DEC 17	CERAB reloaded; updating to resume; current-awareness alerts (SDIs) affected
NEWS	13	DEC 17	THREE NEW FIELDS ADDED TO IFIPAT/IFIUDB/IFICDB
NEWS	14	DEC 30	EPFULL: New patent full text database to be available on STN
NEWS	15	DEC 30	CAPLUS - PATENT COVERAGE EXPANDED
NEWS	16	JAN 03	No connect-hour charges in EPFULL during January and February 2005
NEWS	17	FEB 25	CA/CAPLUS - Russian Agency for Patents and Trademarks (ROSPATENT) added to list of core patent offices covered
NEWS	18	FEB 10	STN Patent Forums to be held in March 2005
NEWS	19	FEB 16	STN User Update to be held in conjunction with the 229th ACS National Meeting on March 13, 2005
NEWS	20	FEB 28	PATDPAFULL - New display fields provide for legal status data from INPADOC
NEWS	21	FEB 28	BABS - Current-awareness alerts (SDIs) available
NEWS	22	FEB 28	MEDLINE/LMEDLINE reloaded
NEWS	23	MAR 02	GBFULL: New full-text patent database on STN
NEWS	24	MAR 03	REGISTRY/ZREGISTRY - Sequence annotations enhanced
NEWS	25	MAR 03	MEDLINE file segment of TOXCENTER reloaded
NEWS	26	MAR 22	KOREAPAT now updated monthly; patent information enhanced
NEWS	27	MAR 22	Original IDE display format returns to REGISTRY/ZREGISTRY
NEWS	28	MAR 22	PATDPASPC - New patent database available
NEWS	29	MAR 22	REGISTRY/ZREGISTRY enhanced with experimental property tags

NEWS EXPRESS	JANUARY 10 CURRENT WINDOWS VERSION IS V7.01a, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 10 JANUARY 2005
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FULL ESTIMATED COST	0.21	0.21

FILE 'CAPLUS' ENTERED AT 15:31:53 ON 25 MAR 2005
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FILE COVERS 1907 - 25 Mar 2005 VOL 142 ISS 14
FILE LAST UPDATED: 24 Mar 2005 (20050324/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> s xanthine oxidase inhibitor
         19530 XANTHINE
          1448 XANTHINES
         19973 XANTHINE
                 (XANTHINE OR XANTHINES)
        111220 OXIDASE
         13166 OXIDASES
        113988 OXIDASE
                 (OXIDASE OR OXIDASES)
        468751 INHIBITOR
        484759 INHIBITORS
        749987 INHIBITOR
                 (INHIBITOR OR INHIBITORS)
L1         708 XANTHINE OXIDASE INHIBITOR
                 (XANTHINE(W)OXIDASE(W)INHIBITOR)

=> s allpurinol
L2           5 ALLPURINOL

=> s allopurinol
          3203 ALLOPURINOL
             8 ALLOPURINOLS
```

```
L3         3203 ALLOPURINOL
                (ALLOPURINOL OR ALLOPURINOLS)

=> e hypertension
E1             2     HYPERTENSIO/BI
E2             3     HYPERTENSIOGENIC/BI
E3         70927 --> HYPERTENSION/BI
E4             1     HYPERTENSION1/BI
E5             1     HYPERTENSION3/BI
E6             2     HYPERTENSION5/BI
E7             3     HYPERTENSIONAL/BI
E8             1     HYPERTENSIONC/BI
E9             1     HYPERTENSIONGENIC/BI
E10            1     HYPERTENSIONN/BI
E11            1     HYPERTENSIONOGENIC/BI
E12            1     HYPERTENSIONOLOGY/BI

=> s e3
          70927 HYPERTENSION/BI
             95 HYPERTENSIONS/BI
L4        70945 HYPERTENSION/BI
                ((HYPERTENSION OR HYPERTENSIONS)/BI)

=> s L4 and L3
L5            66 L4 AND L3

=> s L5 and L1
L6            21 L5 AND L1

=> s L6 and pd<2000
       19742601 PD<2000
                (PD<20000000)
L7             6 L6 AND PD<2000

=> d L7 1-6

L7   ANSWER 1 OF 6  CAPLUS  COPYRIGHT 2005 ACS on STN
AN   1999:231552  CAPLUS
DN   130:249107
TI   System and method for measuring hydrogen peroxide levels in a fluid and
     method for assessing oxidative stress
IN   Lacy, Fred; Schmid-Schonbein, Geert W.; Gough, David
PA   The Regents of the University of California, USA
SO   PCT Int. Appl., 39 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.         DATE
     ---------------     ----   --------    --------------------    --------
PI   WO 9915891           A1     19990401    WO 1998-US19013         19980914 <--
         W:  AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,
             DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG,
             KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX,
             NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,
             UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,
             FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
             CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     AU 9894805            A1     19990412    AU 1998-94805           19980914 <--
PRAI US 1997-60010P        P      19970925
     WO 1998-US19013       W      19980914
RE.CNT  4      THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
               ALL CITATIONS AVAILABLE IN THE RE FORMAT
```

L7 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:350193 CAPLUS
DN 129:93348
TI Nitric oxide exposure inhibits endothelial NOS activity but not gene expression: a role for superoxide
AU Sheehy, A. Macduff; Burson, Michael A.; Black, Stephen M.
CS Department of Pediatrics, University of California, San Francisco, CA, 94143-0106, USA
SO American Journal of Physiology (**1998**), 274(5, Pt. 1), L833-L841
CODEN: AJPHAP; ISSN: 0002-9513
PB American Physiological Society
DT Journal
LA English
RE.CNT 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1996:207673 CAPLUS
DN 124:313438
TI Potentiation of nitric oxide-mediated vasorelaxation by **xanthine oxidase inhibitors**
AU Miyamoto, Yoichi; Akaike, Takaaki; Yoshida, Masaki; Goto, Shingo; Horie, Hidechika; Maeda, Hiroshi
CS School Medicine, Kumamoto Univ., Kumamoto, 860, Japan
SO Proceedings of the Society for Experimental Biology and Medicine (**1996**), 211(4), 366-73
CODEN: PSEBAA; ISSN: 0037-9727
PB Blackwell
DT Journal
LA English

L7 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1995:309509 CAPLUS
DN 122:71419
TI **Allopurinol** fails to protect against gentamicin-induced renal damage in normotensive and spontaneously hypertensive rats
AU Smyth, B.J.; Davis, W.G.
CS Department of Pathology and Laboratory Medicine, Medical University of South Carolina, Charleston, SC, 29425-2645, USA
SO Nephron (**1994**), 68(4), 468-72
CODEN: NPRNAY; ISSN: 0028-2766
DT Journal
LA English

L7 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1993:420255 CAPLUS
DN 119:20255
TI Protective effects of therapy with a protease and **xanthine oxidase inhibitor** in short form pancreatic biliary obstruction and ischemia in rats
AU Hirano, Tetsuya; Manabe, Tadao; Steer, Michael; Printz, Hartmut; Calne, Roy; Tobe, Takayoshi
CS Dep. Surg., Addenbrookes Hosp., Cambridge, UK
SO Surgery, Gynecology and Obstetrics (**1993**), 176(4), 371-81
CODEN: SGOBA9; ISSN: 0039-6087
DT Journal
LA English

L7 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1989:69302 CAPLUS
DN 110:69302
TI The malonyldialdehyde levels in the cerebral tissue after reperfusion following the occlusion of the bilateral common carotid artery in

spontaneously hypertensive rats and the effect of **allopurinol**, a **xanthine oxidase inhibitor**
AU Kawakami, Masato; Itoh, Toru; Tochigi, Shoichiro
CS Sch. Med., St. Marianna Univ., Japan
SO Nosotchu (1988), 10(5), 400-3
CODEN: NOSOD4; ISSN: 0912-0726
DT Journal
LA Japanese

=> d hist

(FILE 'HOME' ENTERED AT 15:31:23 ON 25 MAR 2005)

FILE 'CAPLUS' ENTERED AT 15:31:53 ON 25 MAR 2005
L1 708 S XANTHINE OXIDASE INHIBITOR
L2 5 S ALLPURINOL
L3 3203 S ALLOPURINOL
E HYPERTENSION
L4 70945 S E3
L5 66 S L4 AND L3
L6 21 S L5 AND L1
L7 6 S L6 AND PD<2000

=> d L6 1-21 ABS IBIB

L6 ANSWER 1 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
AB A review. A substantial body of epidemiol. and exptl. evidence suggests that serum uric acid is an important, independent risk factor for cardiovascular and renal disease especially in patients with **hypertension**, heart failure, or diabetes. Elevated serum uric acid is highly predictive of mortality in patients with heart failure or coronary artery disease and of cardiovascular events in patients with diabetes. Further, patients with **hypertension** and hyperuricemia have a 3- to 5-fold increased risk of experiencing coronary artery disease or cerebrovascular disease compared with patients with normal uric acid levels. Although the mechanisms by which uric acid may play a pathogenetic role in cardiovascular disease is unclear, hyperuricemia is associated with deleterious effects on endothelial dysfunction, oxidative metabolism, platelet adhesiveness, hemorheol., and aggregation. **Xanthine oxidase inhibitors** (e.g., **allopurinol**) or a variety of uricosuric agents (e.g., probenecid, sulfinpyrazone, benzbromarone, and benziodarone) can lower elevated uric acid levels but it is unknown whether these agents reversibly impact cardiovascular outcomes. However, the findings of the recent LIFE study in patients with **hypertension** and left ventricular hypertrophy suggest the possibility that a treatment-induced decrease in serum uric acid may indeed attenuate cardiovascular risk. LIFE showed that approx. 29% (14% to 107%, p = 0.004) of the treatment benefit of a losartan-based vs. atenolol-based therapy on the primary composite endpoint (death, myocardial infarction, or stroke) may be ascribed to differences in achieved serum uric acid levels. Overall, serum uric acid may be a powerful tool to help stratify risk for cardiovascular disease. At the very least, it should be carefully considered when evaluating overall cardiovascular risk.
ACCESSION NUMBER: 2004:304720 CAPLUS
DOCUMENT NUMBER: 141:306755
TITLE: Uric acid: role in cardiovascular disease and effects of losartan
AUTHOR(S): Alderman, Michael; Aiyer, Kala J. V.
CORPORATE SOURCE: Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY, USA
SOURCE: Current Medical Research and Opinion (2004), 20(3), 369-379

CODEN: CMROCX; ISSN: 0300-7995
PUBLISHER: LibraPharm Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
REFERENCE COUNT: 93 THERE ARE 93 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

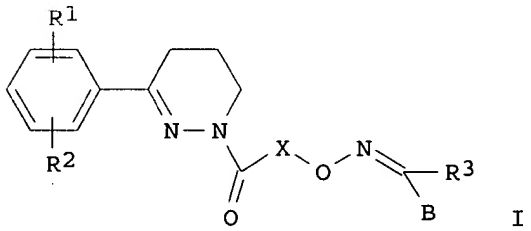
L6 ANSWER 2 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

AB Background: **Allopurinol**, a **xanthine oxidase inhibitor**, and captopril, an inhibitor of angiotensin I-converting enzyme, are widely used for hyperuricemia and **hypertension**, resp. There have been reported cases showing that these two agents are effective for the treatment of granulomatous diseases such as sarcoidosis, although the mode of action is not elucidated. Objectives: We examined the in vitro effects of these agents on the formation of multinucleated giant cells (MGC) from human monocytes by Con A-stimulated mononuclear cell supernatants (conditioned medium). Methods: We cultured monocytes with conditioned medium and each agent and compared the rate of MGC formation as well as the expression of adhesion mols. and P2X7 receptor, which are involved in MGC formation. Results: The addition of 25 or 100 μg mL-1 **allopurinol** or 0.125-1.0 μg mL-1 captopril inhibited MGC formation. Monocytes treated with these agents exhibited less expression of intercellular adhesion mol.-1 (ICAM-1) than untreated monocytes. The susceptibility of monocytes cultured in conditioned medium for 24 h to 2'-and 3'-o-(4-benzoyl-benzoyl)ATP-mediated cytolysis was significantly lower in monocytes treated with these agents than in untreated monocytes. Conclusions: **Allopurinol** and captopril have a therapeutic effect on granulomatous disorders by a direct action on monocyte/macrophage lineage cells partly through down-regulation of ICAM-1 and P2X7 receptor.

ACCESSION NUMBER: 2004:295980 CAPLUS
DOCUMENT NUMBER: 141:325356
TITLE: Inhibitory influences of **xanthine oxidase inhibitor** and angiotensin I-converting enzyme inhibitor on multinucleated giant cell formation from monocytes by down-regulation of adhesion molecules and purinergic receptors
AUTHOR(S): Mizuno, K.; Okamoto, H.; Horio, T.
CORPORATE SOURCE: Department of Dermatology, Kansai Medical University, Moriguchi, Osaka, 570-8507, Japan
SOURCE: British Journal of Dermatology (2004), 150(2), 205-210
CODEN: BJDEAZ; ISSN: 0007-0963
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

GI



I

AB Title compds. [I; R1, R2 = H, OH, OR8, SR8, SOR8, SO2R8, halo; R1R2 = OCH2O, OCH2CH2O; R3 = H, AR7, COAR7, CO2AR7, CONH2, NH2, etc.; R7 = H,

CO2H, NH2, OH, etc.; R8 = (substituted) alkyl, alkenyl, cycloalkyl, alkylenecycloalkyl, etc.; A = null, (O, S, SO, SO2, imino-interrupted) alkylene, alkenylene, cycloalkylene; B = (substituted) aryl, heteroaryl; X = (O, S, SO, SO2, imino-interrupted) alkylene], were prepared as phosphodiesterase IV inhibitors for treating osteoporosis, tumors, cachexia, atherosclerosis, rheumatoid arthritis, multiple sclerosis, diabetes mellitus, inflammatory processes, allergies, asthma, autoimmune diseases, myocardial diseases and AIDS (no data). Thus, 3-(3-ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazine was treated sequentially with chloroacetyl chloride, N-hydroxyphthalimide, ethanolamine, and 4-methoxybenzaldehyde to give 4-methoxybenzaldehyde O-[2-[3-(3-ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-2-oxoethyl]oxime.

ACCESSION NUMBER: 2003:991488 CAPLUS
DOCUMENT NUMBER: 140:27834
TITLE: Preparation of pyridazinyloximes as phosphodiesterase IV inhibitors.
INVENTOR(S): Eggenweiler, Hans-Michael; Beier, Norbert; Schelling, Pierre; Wolf, Michael
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: PCT Int. Appl., 137 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003104205	A1	20031218	WO 2003-EP5173	20030516
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10225574	A1	20031218	DE 2002-10225574	20020610
BR 2003011311	A	20050215	BR 2003-11311	20030516
EP 1511737	A1	20050309	EP 2003-732395	20030516
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				

PRIORITY APPLN. INFO.: DE 2002-10225574 A 20020610
WO 2003-EP5173 W 20030516

OTHER SOURCE(S): MARPAT 140:27834
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
AB The invention discloses the use of type 4 phosphodiesterase inhibitors (PDE IV inhibitors) to treat diseases, as well as combinations of PDE IV inhibitors with other drugs.

ACCESSION NUMBER: 2003:356269 CAPLUS
DOCUMENT NUMBER: 138:348761
TITLE: Type 4 phosphodiesterase inhibitors and therapeutic uses thereof
INVENTOR(S): Eggenweiler, Hans-Michael; Wolf, Michael
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: PCT Int. Appl., 122 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003037342	A1	20030508	WO 2002-EP9596	20020828
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1463509	A1	20041006	EP 2002-802281	20020828
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
US 2004259863	A1	20041223	US 2004-494379	20040430
PRIORITY APPLN. INFO.:			EP 2001-125394 A	20011031
			WO 2002-EP9596 W	20020828

OTHER SOURCE(S): MARPAT 138:348761
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 5 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

AB Angiotensin II-induced **hypertension** is associated with NAD(P)H oxidase-dependent superoxide production in the vessel wall. Vascular superoxide level is also increased in deoxycorticosterone acetate (DOCA)-salt **hypertension**, which is associated with a markedly depressed plasma renin activity because of sodium retention. However, the mechanisms underlying superoxide production in low-renin **hypertension** are undefined. This study investigated (1) whether and how endothelin-1 (ET-1), which is increased in DOCA-salt hypertensive rats, contributes to arterial superoxide generation and (2) the effect of gene transfer of manganese superoxide dismutase and endothelial nitric oxide synthase. Both superoxide and ET-1 levels were significantly elevated in carotid arteries of DOCA-salt rats compared with that of the sham-operated controls. ET-1 concentration-dependently stimulated superoxide production in vitro in carotid arteries of normotensive rats. The increase in arterial superoxide in both ET-1-treated normotensive and DOCA-salt rats was reversed by a selective ETA receptor antagonist, ABT-627, the flavoprotein inhibitor diphenyleneiodonium, and the NADPH oxidase inhibitor apocynin but not by the nitric oxide synthase inhibitor Nω-L-arginine Me ester or the **xanthine oxidase inhibitor allopurinol**. Furthermore, in vivo blockade of ETA receptors significantly reduced arterial superoxide levels, with a concomitant decrease of systolic blood pressure in DOCA-salt rats. Ex vivo gene transfer of manganese superoxide dismutase or endothelial nitric oxide synthase also suppressed superoxide levels in carotid arteries of DOCA-salt rats. These findings suggest that ET-1 augments vascular superoxide production at least in part via an ETA/NADPH oxidase pathway in low-renin mineralocorticoid **hypertension**.

ACCESSION NUMBER: 2003:328016 CAPLUS
DOCUMENT NUMBER: 138:366815
TITLE: Endothelin-1 increases vascular superoxide via endothelinA-NADPH oxidase pathway in low-renin **hypertension**
AUTHOR(S): Li, Lixin; Fink, Gregory D.; Watts, Stephanie W.; Northcott, Carrie A.; Galligan, James J.; Pagano, Patrick J.; Chen, Alex F.

CORPORATE SOURCE: Department of Pharmacology and Toxicology, Michigan State University, East Lansing, MI, USA
SOURCE: Circulation (2003), 107(7), 1053-1058
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 6 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

AB Hyperuricemia is associated with renal disease, but it is usually considered a marker of renal dysfunction rather than a risk factor for progression. Recent studies have reported that mild hyperuricemia in normal rats induced by the uricase inhibitor, oxonic acid (OA), results in **hypertension**, intrarenal vascular disease, and renal injury. This led to the hypothesis that uric acid may contribute to progressive renal disease. To examine the effect of hyperuricemia on renal disease progression, rats were fed 2% OA for 6 wk after 5/6 remnant kidney (RK) surgery with or without the **xanthine oxidase inhibitor**, **allopurinol**, or the uricosuric agent, benziodarone. Renal function and histol. studies were performed at 6 wk. Given observations that uric acid induces vascular disease, the effect of uric acid on vascular smooth muscle cells in culture was also examined RK rats developed transient hyperuricemia (2.7 mg/dL at week 2), but then levels returned to baseline by week 6 (1.4 mg/dL). In contrast, RK+OA rats developed higher and more persistent hyperuricemia (6 wk, 3.2 mg/dL). Hyperuricemic rats demonstrated higher BP, greater proteinuria, and higher serum creatinine than RK rats. Hyperuricemic RK rats had more renal hypertrophy and greater glomerulosclerosis (24.2 ± 2.5 vs. 17.5 ± 3.4%; $P < 0.05$) and interstitial fibrosis (1.89 ± 0.45 vs. 1.52 ± 0.47; $P < 0.05$). Hyperuricemic rats developed vascular disease consisting of thickening of the preglomerular arteries with smooth muscle cell proliferation; these changes were significantly more severe than a historical RK group with similar BP. **Allopurinol** significantly reduced uric acid levels and blocked the renal functional and histol. changes. Benziodarone reduced uric acid levels less effectively and only partially improved BP and renal function, with minimal effect on the vascular changes. To better understand the mechanism for the vascular disease, the expression of COX-2 and renin were examined Hyperuricemic rats showed increased renal renin and COX-2 expression, the latter especially in preglomerular arterial vessels. In in vitro studies, cultured vascular smooth muscle cells incubated with uric acid also generated COX-2 with time-dependent proliferation, which was prevented by either a COX-2 or TXA-2 receptor inhibitor. Hyperuricemia accelerates renal progression in the RK model via a mechanism linked to high systemic BP and COX-2-mediated, thromboxane-induced vascular disease. These studies provide direct evidence that uric acid may be a true mediator of renal disease and progression.

ACCESSION NUMBER: 2002:870447 CAPLUS
DOCUMENT NUMBER: 138:236192
TITLE: A Role for Uric Acid in the Progression of Renal Disease
AUTHOR(S): Kang, Duk-Hee; Nakagawa, Takahiko; Feng, Lili; Watanabe, Susumu; Han, Lin; Mazzali, Marilda; Truong, Luan; Harris, Raymond; Johnson, Richard J.
CORPORATE SOURCE: Division of Nephrology, Baylor College of Medicine, Houston, Texas, USA
SOURCE: Journal of the American Society of Nephrology (2002), 13(12), 2888-2897
CODEN: JASNEU; ISSN: 1046-6673
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 7 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

AB The purpose of this study was the evaluation of the xanthine oxidase (XO) inhibition produced by some synthetic 2-styrylchromones. Ten polyhydroxylated derivs. with several substitution patterns were synthesized, and these and a pos. control, **allopurinol**, were tested for their effects on XO activity by measuring the formation of uric acid from xanthine. The synthesized 2-styrylchromones inhibited xanthine oxidase in a concentration-dependent and non-competitive manner. Some IC50 values found were as low as 0.55 μM, which, by comparison with the IC50 found for **allopurinol** (5.43 μM), indicates promising new inhibitors. Those 2-styrylchromones found to be potent XO inhibitors should be further evaluated as potential agents for the treatment of pathologies related to the enzyme's activity, as is the case of gout, ischemia/reperfusion damage, **hypertension**, hepatitis and cancer.

ACCESSION NUMBER: 2002:673856 CAPLUS
DOCUMENT NUMBER: 138:214866
TITLE: 2-Styrylchromones as novel inhibitors of xanthine oxidase. A structure-activity study
AUTHOR(S): Fernandes, Eduarda; Carvalho, Felix; Silva, Artur M. S.; Santos, Clementina M. M.; Pinto, Diana C. G. A.; Cavaleiro, Jose A. S.; De Lourdes Bastos, Maria
CORPORATE SOURCE: ICETA/CEQUP, Toxicology Department, Faculty of Pharmacy, University of Porto-Rua Anibal Cunha, Oporto, 4050-047, Port.
SOURCE: Journal of Enzyme Inhibition and Medicinal Chemistry (2002), 17(1), 45-48
CODEN: JEIMAZ; ISSN: 1475-6366
PUBLISHER: Taylor & Francis Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 8 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title compds. [I; g = 0-1; j = 0-1; provided that when j = 0, n must be 2; k = 0-1; m = 0-2; n = 1-2; W1 = 0, SOt (t = 0-2), NR3; W2 = OCR9R10, or absent; Y = CR1, NOk (k = 0-1); R9, R10 = H, F, CF3, etc.; or R9 and R10 are taken together, but only in the case where m = 1, to form a spiro moiety; R7, R8 have the same meaning as R9, R10 except that one of them must be H; R1, R2 = H, F, Cl, etc.; R3 = H, alkyl, Ph, etc.; R4-R6 = H, F, Cl, etc.; Q1 = Ph, benzodioxyl, etc.; Q2 = biaryl moiety], useful as inhibitors of PDE4 in the treatment of diseases regulated by the activation and degranulation of eosinophils, especially asthma, chronic bronchitis, and chronic obstructive pulmonary disease, were prepared E.g., a multi-step synthesis of the amide II, starting from Me 3-bromobenzoate and 4-formylbenzeneboronic acid, was given. Compds. I showed anti-inflammatory activity at 0.0001 μM to 20.0 μM in whole blood assay for LTE4.

ACCESSION NUMBER: 2002:594822 CAPLUS
DOCUMENT NUMBER: 137:154857
TITLE: Preparation of nicotinamide biaryl derivatives as inhibitors of PDE4 isozymes
INVENTOR(S): Chambers, Robert James; Magee, Thomas Victor; Marfat, Anthony

PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: PCT Int. Appl., 224 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2002060875	A1	20020808	WO 2001-IB2341		20011206
WO 2002060875	C1	20030731			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2436535	AA	20020808	CA 2001-2436535		20011206
EP 1355884	A1	20031029	EP 2001-273556		20011206
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
EE 200300360	A	20031215	EE 2003-360		20011206
BR 2001016852	A	20040225	BR 2001-16852		20011206
JP 2004520386	T2	20040708	JP 2002-561026		20011206
NZ 526453	A	20050128	NZ 2001-526453		20011206
US 2002193612	A1	20021219	US 2002-62813		20020131
US 6649633	B2	20031118			
ZA 2003004894	A	20040624	ZA 2003-4894		20030624
US 2004048903	A1	20040311	US 2003-613988		20030702
BG 108038	A	20040730	BG 2003-108038		20030728
NO 2003003397	A	20030919	NO 2003-3397		20030730
PRIORITY APPLN. INFO.:			US 2001-265492P	P	20010131
			WO 2001-IB2341	W	20011206
			US 2002-62813	A3	20020131

OTHER SOURCE(S): MARPAT 137:154857
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 9 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
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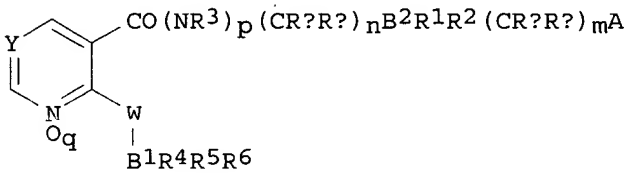

I

AB Title compds. [I; p, q = 0, 1; m = 0-2; n = 1, 2; A = CO2R7, CONR9CO2R7, CONR7R9, OP(O)(OH)2, SO3H, acylsulfonamido, etc.; W = O, S, SO, SO2, NR3; Y = N, NO, CR11; R1, R2 = H, F, Cl, cyano, NO2, alkyl, alkynyl, fluoroalkyl, etc.; R3 = H, alkyl, Ph, PhCH2, etc.; R4-R6 = H, F, Cl, alkynyl, cyano, NO2, etc.; R7 = H, (substituted) alkyl, alkenyl, alkynyl; R9 = H, alkyl, cycloalkyl, Ph, PhCH2, pyridyl, etc.; R11 = H, F, Cl, cyano, NO2, alkyl, alkynyl, fluoroalkyl, fluoroalkoxy, etc.; Ra, Rb = H, F, CF3, alkyl, (substituted) cycloalkyl, Ph, PhCH2; B1, B2 = 3-7 membered

(hetero)cyclyl, 7-12 membered poly(hetero)cyclyl; pairs of variables may form rings; with provisos], were prepared (no data). Thus, Me 2-[4-[[[2-(benzo[1,3]dioxol-5-yloxy)pyridine-3-carbonyl]amino]methyl]phenyl]-2-methylpropionate was suspended in Me3COH. Aqueous NaOH was added to the suspension, and the reaction mixture was refluxed 1 h to give 2-[4-[[[2-(benzo[1,3]dioxol-5-yloxy)pyridine-3-carbonyl]amino]methyl]phenyl]-2-methylpropionic acid.

ACCESSION NUMBER: 2002:591707 CAPLUS
DOCUMENT NUMBER: 137:140509
TITLE: Preparation of nicotinamides and mimetics as inhibitors of phosphodiesterase IV isozymes
INVENTOR(S): Chambers, Robert J.; Magee, Thomas V.; Marfat, Anthony
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: Eur. Pat. Appl., 180 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1229034	A1	20020807	EP 2002-250202	20020111
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
CA 2369462	AA	20020731	CA 2002-2369462	20020129
US 2002111495	A1	20020815	US 2002-62811	20020131
BR 2002000250	A	20021008	BR 2002-250	20020131
US 2004171798	A1	20040902	US 2004-781062	20040217

PRIORITY APPLN. INFO.:
US 2001-265240P P 20010131
US 1997-43403P P 19970404
US 1998-105120P P 19981021
US 2002-62811 B1 20020131.

OTHER SOURCE(S): MARPAT 137:140509
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 10 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
AB This invention relates to a method for treating and preventing **hypertension** by administering a therapeutically effective amount of an agent capable of reducing uric acid levels in a patient in need of such treatment. Addnl., the scope of the invention includes a method of treating coronary heart disease by administering a therapeutically effective amount of an agent capable of reducing uric acid levels in a patient in need of such treatment. **Allopurinol** administered from the initiation of an oxonic acid diet prevented the development of hyperuricemia and **hypertension**. In hypertensive, hyperuricemic rats, either withdrawal of the oxonic acid or adding **allopurinol** also resulted in a reduction in the blood pressure in association with a fall in serum uric acid values.

ACCESSION NUMBER: 2002:10270 CAPLUS
DOCUMENT NUMBER: 136:64126
TITLE: Agent reducing uric acid levels for treatment of cardiovascular disease and **hypertension**
INVENTOR(S): Kivlighn, Salah; Johnson, Richard J.; Mazzali, Marilda
PATENT ASSIGNEE(S): Merck & Co., Inc., USA; University of Washington
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2002000210	A2	20020103	WO 2001-US20457		20010628
WO 2002000210	A3	20021024			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
CA 2413201	AA	20020103	CA 2001-2413201		20010628
US 2002019360	A1	20020214	US 2001-892505		20010628
EP 1317258	A2	20030611	EP 2001-946722		20010628
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2004517804	T2	20040617	JP 2002-504992		20010628
PRIORITY APPLN. INFO.:			US 2000-214825P	P	20000628
			WO 2001-US20457	W	20010628

L6 ANSWER 11 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

AB We previously reported increased aortic reactive oxygen species (ROS) production in mineralocorticoid (deoxycorticosterone acetate [DOCA]-salt) hypertensive rats. In the present study, we tested the hypothesis that NADH/NADPH oxidase is responsible for increased ROS production, namely superoxide (O2-), in aorta from the DOCA-salt rat. Treatment of aortic rings from DOCA-salt rats with the NO synthase inhibitor N-nitro-L-arginine and the **xanthine oxidase inhibitor allopurinol** did not significantly change O2- production Furthermore, de-endothelialization of aorta from DOCA-salt rats did not affect O2- production compared with that of sham-operated rats. Thus, xanthine oxidase and uncoupled endothelial NO synthase were not responsible for increased O2- production in the DOCA-salt rats. In contrast, treatment with the NADPH oxidase inhibitor apocynin significantly decreased O2- production in aortic rings from DOCA-salt rats compared with sham-operated rats. Moreover, long-term administration of apocynin (in drinking water, 1.5 mmol/L, 28 days) to DOCA-salt rats significantly decreased systolic blood pressure compared with that of rats treated with DOCA-salt alone. Furthermore, O2- production in aortic rings from DOCA-salt rats treated with apocynin for 28 days was reduced compared with that of untreated DOCA-salt rats. Reverse transcriptase-polymerase chain reaction (RT-PCR) anal. demonstrated that DOCA-salt rats have significantly greater mRNA levels of the NADPH oxidase subunit p22phox than do sham-operated rats. These findings suggest that NADPH oxidase is increased and is responsible for increased O2- production and possibly contributes to increased blood pressure in the DOCA-salt hypertensive rat.

ACCESSION NUMBER: 2001:887837 CAPLUS
DOCUMENT NUMBER: 136:148868
TITLE: NADH/NADPH oxidase and enhanced superoxide production in the mineralocorticoid hypertensive rat
AUTHOR(S): Beswick, Richard A.; Dorrance, Anne M.; Leite, Romulo; Webb, R. Clinton
CORPORATE SOURCE: Department of Physiology, University of Michigan, Ann Arbor, MI, USA
SOURCE: Hypertension (2001), 38(5), 1107-1111
CODEN: HPRTDN; ISSN: 0194-911X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 12 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

AB An elevation in circulating serum uric acid is strongly associated with the development of **hypertension** and renal disease, but whether uric acid has a causal role or whether it simply indicates patients at risk for these complications remains controversial. We tested the hypothesis that uric acid may have a causal role in the development of hypertension and renal disease by examining the effects of mild hyperuricemia in rats. Mild hyperuricemia was induced in rats by providing a uricase inhibitor (oxonic acid) in the diet. Hyperuricemic rats developed elevated blood pressure after 3 wk, whereas control rats remained normotensive. The development of **hypertension** was prevented by concurrent treatment with either a **xanthine oxidase inhibitor** (**allopurinol**) or a uricosuric agent (benziodarone), both of which lowered uric acid levels. Blood pressure could also be lowered by reducing uric acid levels with either **allopurinol** or oxonic acid withdrawal. A direct relationship was found between blood pressure and uric acid (r=0.75, n=69), with a 10-mm Hg blood pressure increase for each 0.03-mmol/L (0.5-mg/dL) incremental rise in serum uric acid. The kidneys were devoid of urate crystals and were normal by light microscopy. However, immunohistochem. stains documented an ischemic type of injury with collagen deposition, macrophage infiltration, and an increase in tubular expression of osteopontin. Hyperuricemic rats also exhibited an increase in juxtaglomerular renin and a decrease in macula densa neuronal NO synthase. Both the renal injury and **hypertension** were reduced by treatment with enalapril or L-arginine. In conclusion, mild hyperuricemia causes **hypertension** and renal injury in the rat via a crystal-independent mechanism, with stimulation of the renin-angiotensin system and inhibition of neuronal NO synthase.

ACCESSION NUMBER: 2001:887836 CAPLUS
DOCUMENT NUMBER: 136:148867
TITLE: Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism
AUTHOR(S): Mazzali, Marilda; Hughes, Jeremy; Kim, Yoon-Goo; Jefferson, J. Ashley; Kang, Duk-Hee; Gordon, Katherine L.; Lan, Hui Y.; Kivlighn, Salah; Johnson, Richard J.
CORPORATE SOURCE: Division of Nephrology, University of Washington Medical Center, Seattle, WA, USA
SOURCE: Hypertension (2001), 38(5), 1101-1106
CODEN: HPRTDN; ISSN: 0194-911X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 13 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

AB The invention relates to novel methods using, and pharmaceutical compns. and dosage forms comprising, sertindole derivs. Sertindole derivs. include, but are not limited to, nor-sertindole, 5-oxo-sertindole, dehydro-sertindole, and dehydro-nor-sertindole. The methods of the invention are directed to the treatment and prevention of neuroleptic and related disorders such as, but are not limited to, psychotic disorders, depression, anxiety, substance addiction, memory impairment and pain. For example, capsules were prepared containing a sertindole derivative 50.0 mg, lactose 48.5 mg, TiO2 0.5 mg, and Mg stearate 1.0 mg.

ACCESSION NUMBER: 2000:861482 CAPLUS
DOCUMENT NUMBER: 134:32977
TITLE: Methods and compositions for the treatment of neuroleptic and related disorders using sertindole derivatives
INVENTOR(S): Jerussi, Thomas P.
PATENT ASSIGNEE(S): Sepracor Inc., USA

SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000072837	A2	20001207	WO 2000-US14984	20000531
WO 2000072837	A3	20010517		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6489341	B1	20021203	US 2000-580492	20000530
PRIORITY APPLN. INFO.:			US 1999-137447P P	19990602
			US 2000-580492 A	20000530

L6 ANSWER 14 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

AB A method of treating weight loss due to underlying disease in a patient, the method comprising administering to the patient an effective amount of an agent which reduces sympathetic nervous system activity. A method of treating weight loss due to underlying disease in a patient, the method comprising administering to the patient an effective amount of any one or more of the following: a compound which inhibits the effect of aldosterone such as an aldosterone antagonist; a chymase inhibitor; a cathepsin B inhibitor; a β receptor blocker; an imidazoline receptor antagonist; a centrally acting α receptor antagonist; a peripherally acting α receptor antagonist; a ganglion blocking agent; a drug that has an effect on cardiovascular reflexes and thereby reduces SNS activity such as an opiate; scopolamine; an endothelin receptor antagonist; and a **xanthine oxidase inhibitor**. The methods are particularly useful in treating cardiac cachexia. The sympathetic nervous system activity-reducing agents may also be used to treat weight loss due to aging and to enhance exercise performance.

ACCESSION NUMBER: 2000:259979 CAPLUS
DOCUMENT NUMBER: 132:288794
TITLE: Sympathetic nervous system activity-reducing agents for treatment of disease- or age-related weight loss and for enhancement of exercise performance
INVENTOR(S): Anker, Stefan Dietmar; Coats, Andrew Justin Stewart
PATENT ASSIGNEE(S): Imperial College Innovations Limited, UK
SOURCE: PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000021509	A2	20000420	WO 1999-GB3302	19991015
WO 2000021509	A3	20001109		
W: JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1121111	A2	20010808	EP 1999-947762	19991015
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

IE, FI

JP 2002527378	T2	20020827	JP 2000-575485		19991015
PRIORITY APPLN. INFO.:			GB 1998-22458	A	19981015
			GB 1998-22459	A	19981015
			GB 1999-17181	A	19990723
			WO 1999-GB3302	W	19991015

L6 ANSWER 15 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

AB Therapeutic strategies against free radicals have mostly focused on the augmentation of antioxidant defenses (eg, vitamins C and E). A novel approach is to prevent free radical generation by the enzyme system xanthine oxidase. We examined whether the inhibition of xanthine oxidase with **allopurinol** can improve endothelial function in subjects with type 2 diabetes and coexisting mild **hypertension** compared with control subjects of a similar age. We examined 23 subjects (11 patients with type 2 diabetes and 12 healthy age-matched control subjects) in 2 parallel groups. The subjects were administered 300 mg **allopurinol** in a randomized, placebo-controlled study in which both therapies were administered for 1 mo. Endothelial function was assessed with bilateral venous occlusion plethysmog., in which the forearm blood flow responses to intra-arterial infusions of endothelium-dependent and -independent vasodilators were measured. **Allopurinol** significantly increased the mean forearm blood flow response to acetylcholine by 30% (3.16±1.21 vs. 2.54±0.76 mL · 100 mL-1 · min-1 **allopurinol** vs. placebo; P=0.012, 95% CI 0.14, 1.30) but did not affect the nitroprusside response in patients with type 2 diabetes. There was no significant impact on either endothelium-dependent or -independent vascular responses in age-matched control subjects. **Allopurinol** improved endothelial function to near-normal levels. Regarding markers of free radical activity, the level of malondialdehyde was significantly reduced (0.30±0.04 vs. 0.34±0.05 μmol/L for **allopurinol** vs. placebo, P=0.03) in patients with type 2 diabetes but not in control subjects. The **xanthine oxidase inhibitor allopurinol** improves endothelial dysfunction in patients with type 2 diabetes with mild **hypertension** but not in matched control subjects. In the former group, **allopurinol** restored endothelial function to near-normal levels.

ACCESSION NUMBER:	2000:229952 CAPLUS
DOCUMENT NUMBER:	132:260495
TITLE:	**Allopurinol** normalizes endothelial dysfunction in type 2 diabetics with mild **hypertension**
AUTHOR(S):	Butler, Robert; Morris, Andrew D.; Belch, Jill J. F.; Hill, Alexander; Struthers, Allan D.
CORPORATE SOURCE:	University Department of Clinical Pharmacology and Therapeutics, Ninewells Hospital and Medical School, Dundee, DD1 9SY, UK
SOURCE:	Hypertension (2000), 35(3), 746-751 CODEN: HPRTDN; ISSN: 0194-911X
PUBLISHER:	Lippincott Williams & Wilkins
DOCUMENT TYPE:	Journal
LANGUAGE:	English
REFERENCE COUNT:	41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 16 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

AB The detection system includes a pair of electrochem. hydrogen peroxide sensors, each sensor having working, counter and reference electrodes. A bias voltage is applied to maintain a voltage difference between the working and reference electrodes. A sample aliquot of fluid was treated with either sodium azide or catalase. The sensors are placed in containers containing sufficient amts. of treated fluid to cover the active portions of the electrodes. The output current of each sensor is amplified, and the

resulting amplified signals are combined and subtracted to provide a signal which is representative of the level of hydrogen peroxide in the fluid. In a method for assessing oxidative stress, including that related to essential **hypertension**, the detection system is used to determine a representative level of hydrogen peroxide in blood plasma drawn from a test subject. The level of hydrogen peroxide is directly related to the level of reactive oxygen species in the plasma, and can be used as an accurate predictor of risk for essential hypertension or other conditions related to oxidative stress. Blood plasma samples of normotensive subjects and patients with essential **hypertension** were analyzed by the system. When hypertensives were compared with family history neg. normotensives, it was found that the hypertensive group had a higher mean arterial pressure by 23% as well as higher levels of plasma hydrogen peroxide by 48% over the normotensive control.

ACCESSION NUMBER: 1999:231552 CAPLUS
DOCUMENT NUMBER: 130:249107
TITLE: System and method for measuring hydrogen peroxide levels in a fluid and method for assessing oxidative stress
INVENTOR(S): Lacy, Fred; Schmid-Schonbein, Geert W.; Gough, David
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9915891	A1	19990401	WO 1998-US19013		19980914
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
AU 9894805	A1	19990412	AU 1998-94805		19980914
PRIORITY APPLN. INFO.:			US 1997-60010P	P	19970925
			WO 1998-US19013	W	19980914

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 17 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
AB Recent studies have characterized a rebound pulmonary vasoconstriction with abrupt withdrawal of inhaled nitric oxide (NO) during therapy for pulmonary **hypertension**, suggesting that inhaled NO may downregulate basal NO production However, the exact mechanism of this rebound pulmonary **hypertension** remains unclear. The objectives of these studies were to determine the effect of NO exposure on endothelial NO synthase (eNOS) gene expression, enzyme activity, and posttranslational modification in cultured pulmonary arterial endothelial cells. Sodium nitroprusside (SNP) treatment had no effect on eNOS mRNA or protein levels but did produce a significant decrease in enzyme activity. Furthermore, although SNP treatment induced protein kinase C (PKC)-dependent eNOS phosphorylation, blockade of PKC activity did not protect against the effects of SNP. When the **xanthine oxidase inhibitor allopurinol** or the superoxide scavenger 4,5-dihydroxy-1-benzene-disulfonic acid were co-incubated with SNP, the inhibitory effects on eNOS activity could be partially alleviated. Also, the levels of superoxide were found to be elevated 4.5-fold when cultured pulmonary arterial endothelial cells were exposed to the NO donor

spermine/NO. This suggests that NO can stimulate xanthine oxidase to cause an increase in cellular superoxide generation. A reaction between NO and superoxide would produce peroxynitrite, which could then react with the eNOS protein, resulting in enzyme inactivation. This mechanism may explain, at least in part, how NO produces NOS inhibition in vivo and may delineate, in part, the mechanism of rebound pulmonary hypertension after withdrawal of inhaled NO.

ACCESSION NUMBER: 1998:350193 CAPLUS
DOCUMENT NUMBER: 129:93348
TITLE: Nitric oxide exposure inhibits endothelial NOS activity but not gene expression: a role for superoxide
AUTHOR(S): Sheehy, A. Macduff; Burson, Michael A.; Black, Stephen M.
CORPORATE SOURCE: Department of Pediatrics, University of California, San Francisco, CA, 94143-0106, USA
SOURCE: American Journal of Physiology (1998), 274(5, Pt. 1), L833-L841
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 18 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

AB Nitric oxide (NO), now almost synonymous with endothelium-derived relaxing factor (EDRF), reacts with superoxide anion radical (O2-) and forms a potentially toxic mol. species, peroxynitrite (ONOO-). Because xanthine oxidase (XO) seems to be a major O2--producing enzyme in the vascular system, it is important to clarify the mechanism of XO regulation of NO/EDRF. We first characterized the inhibition of XO in vitro by three types of pyrazolopyrimidine derivs. Kinetic studies indicated that 4-amino-6-hydroxypyrazolo[3,4-d]pyrimidine (AHPP) and **allopurinol** competitively inhibited the conversion of xanthine to uric acid catalyzed by XO, with apparent Ki values of 0.17 ± 0.02 and 0.50 ± 0.03 μM, resp.; alloxanthine inhibited this conversion in a noncompetitive manner with an apparent Ki value of 3.54 ± 1.12 μM. O2- generation in the xanthine/XO system assayed by lucigenin-dependent chemiluminescence was suppressed most strongly by AHPP in a dose-dependent fashion; **allopurinol** itself appears to reduce the enzyme by transfer of an electron to O2, thus generating O2-. AHPP significantly augmented EDRF-mediated relaxation of aortic rings from both rabbits and spontaneously hypertensive rats (SHR) in a dose-dependent manner, whereas allopurinol did not affect the relaxation and only marginal potentiation of the vasorelaxation was observed with alloxanthine. Finally, i.v. injection of AHPP (50.4 mg/kg; 100 μmol/300 g rat) reduced the blood pressure of SHR rats to 70% of the initial pressure; this pressure is almost the blood pressure of normal rats. **Allopurinol** (100 μmol/300 g rat; i.v.) showed transient decrease in blood pressure and moderate reduction of **hypertension** of SHR (10%) was observed with i.v. injection of alloxanthine (100 μmol/300 g rat). On the basis of these results, it seems that XO regulates EDRF/NO via production of O2-.

ACCESSION NUMBER: 1996:207673 CAPLUS
DOCUMENT NUMBER: 124:313438
TITLE: Potentiation of nitric oxide-mediated vasorelaxation by **xanthine oxidase inhibitors**
AUTHOR(S): Miyamoto, Yoichi; Akaike, Takaaki; Yoshida, Masaki; Goto, Shingo; Horie, Hidechika; Maeda, Hiroshi
CORPORATE SOURCE: School Medicine, Kumamoto Univ., Kumamoto, 860, Japan
SOURCE: Proceedings of the Society for Experimental Biology and Medicine (1996), 211(4), 366-73
CODEN: PSEBAA; ISSN: 0037-9727

QP1.38

PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English

L6 ANSWER 19 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
AB Recent research suggests the involvement of hydroxyl and superoxide free radicals in the development of gentamicin induced acute renal tubular necrosis. Xanthine oxidase has been implicated as an important source of superoxide free radicals. Spontaneously hypertensive (Wistar-Kyoto) rats (SHR) have excessive oxidant stress which may render them more sensitive to the reported oxygen free radical producing effects of gentamicin. This study was undertaken to determine if the **xanthine oxidase inhibitor allopurinol** will ameliorate the effects of gentamicin. Normotensive Wistar-Kyoto (WKY) rats and SHR were administered **allopurinol** (40 mg/kg twice daily) orally 4 days before and throughout a 12-day gentamicin treatment period. The **allopurinol** only treatment group demonstrated no noticeable histol. or functional changes considered to be indicative of nephrotoxicity. Gentamicin-injected WKY rats and SHR equally demonstrated extensive proximal tubular and glomerular damage characteristic of aminoglycoside-induced kidney damage. **Allopurinol** failed to protect either rat strain against the histol. damage caused by gentamicin. Equivalent alterations in serum creatinine, serum gentamicin, urinary N-acetyl-β-D-glucos-aminidase excretion, body weight, urinary output, and blood pressure occurred in the gentamicin with **allopurinol** and gentamicin only treatment groups. Our results demonstrate **allopurinol** does not ameliorate the pathogenesis of gentamicin-induced renal damage. SHR do not appear to be more sensitive to the effects of gentamicin-induced kidney damage with or without **allopurinol** as compared with WKY rats.
ACCESSION NUMBER: 1995:309509 CAPLUS
DOCUMENT NUMBER: 122:71419
TITLE: **Allopurinol** fails to protect against gentamicin-induced renal damage in normotensive and spontaneously hypertensive rats
AUTHOR(S): Smyth, B.J.; Davis, W.G.
CORPORATE SOURCE: Department of Pathology and Laboratory Medicine, Medical University of South Carolina, Charleston, SC, 29425-2645, USA
SOURCE: Nephron (1994), 68(4), 468-72
CODEN: NPRNAY; ISSN: 0028-2766
DOCUMENT TYPE: Journal
LANGUAGE: English

L6 ANSWER 20 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
AB The current study was done to evaluate the effects of short term (60 min) pancreatic biliary duct obstruction (PBDO) with intraductal **hypertension** (IDH) stimulated by secretin (0.2 clin. unit per kg per h) and caerulein (0.2 μg per kg per h) plus 30 min of temporary pancreatic ischemia (ISCH) produced by ligation of celiac and superior mesenteric artery on the exocrine pancreas and protective effects of a new potent protease inhibitor, ONO3307 in combination with **xanthine oxidase inhibitor, allopurinol**, in this multifactor related model of acute pancreatitis in rats. 12 H after PBDO with IDH plus ISCH, we observed hyperamylasemia; pancreatic edema into the pancreatic juice of rats stimulated by caerulein (control group-serum amylase levels, 6 ± 1 units per mL; pancreatic water content, 74 ± 1 percent. Furthermore, PBDO with IDH plus ISCH caused the redistribution of lysosomal enzyme from lysosomal fraction to zymogen fraction. Only PBDO with IDH caused no significant changes. Although only ONO3307 or **allopurinol** therapy showed the partial significant protective effects against pancreatic injuries, improving serum amylase levels, the administration of ONO3307 in combination therapy with **allopurinol** showed almost complete protective effects against the pancreatic injuries

induced by PBDO with IDH plus ISCH (serum amylase levels, 9 ± 2 units per mL; pancreatic water content, 76 ± 2 percent; amylase and cathepsin B output, 7,127 ± 946 and 18 ± 3 units per kg per h; 1.3 kilo times gravity pellet, 28 ± 2 percent; 12 kilo times gravity pellet, 54 ± 2 percent, and energy charge equals 0.85 ± 0.02). These results indicate the important roles of temporary pancreatic ischemia and oxygen derived free radicals in the pathogenesis of pancreatic damages in this PBDO with IDH plus ISCH reperfusion in the rat model and the usefulness of combination therapy of such a new potent protease inhibitor and **xanthine oxidase inhibitor**, such as **allopurinol**, in the treatment of clin. acute pancreatitis.

ACCESSION NUMBER: 1993:420255 CAPLUS
DOCUMENT NUMBER: 119:20255
TITLE: Protective effects of therapy with a protease and **xanthine oxidase inhibitor** in short form pancreatic biliary obstruction and ischemia in rats
AUTHOR(S): Hirano, Tetsuya; Manabe, Tadao; Steer, Michael; Printz, Hartmut; Calne, Roy; Tobe, Takayoshi
CORPORATE SOURCE: Dep. Surg., Addenbrookes Hosp., Cambridge, UK
SOURCE: Surgery, Gynecology and Obstetrics (1993), 176(4), 371-81
CODEN: SGOBA9; ISSN: 0039-6087
DOCUMENT TYPE: Journal
LANGUAGE: English

L6 ANSWER 21 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
AB Using spontaneously hypertensive rats, the authors studied the effect of **allopurinol**, a **xanthine oxidase inhibitor**, on lipid peroxidn. in the cerebral tissue after reperfusion for 30 min following the occlusion of the bilateral common carotid artery for 3 h. In the present study, the malonyldialdehyde (MDA) values were measured as indicators for lipid peroxides in the cerebral tissue, and compared them between the group pretreated with oral administrations of **allopurinol** (400 mg/kg) and the nontreated control group. As a result, the MDA value measured were found to be 68.9 nmol/gm in the Sham-operated group and 83.27 nmol/gm in the control group. However, the **allopurinol**-treated group showed a level as low as 67.62 nmol/gm which was significant compared to that of the control group. These results suggest the possibility that **allopurinol** inhibits the lipid peroxidn. caused by the xanthine oxidase-linked free radical induced by cerebral ischemia and reperfusion.

ACCESSION NUMBER: 1989:69302 CAPLUS
DOCUMENT NUMBER: 110:69302
TITLE: The malonyldialdehyde levels in the cerebral tissue after reperfusion following the occlusion of the bilateral common carotid artery in spontaneously hypertensive rats and the effect of **allopurinol**, a **xanthine oxidase inhibitor**
AUTHOR(S): Kawakami, Masato; Itoh, Toru; Tochigi, Shoichiro
CORPORATE SOURCE: Sch. Med., St. Marianna Univ., Japan
SOURCE: Nosotchu (1988), 10(5), 400-3
CODEN: NOSOD4; ISSN: 0912-0726
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

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       3954637 ACID
       1469590 ACIDS
       4430938 ACID
                 (ACID OR ACIDS)
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         96545 LOWERING
           241 LOWERINGS
         96683 LOWERING
                 (LOWERING OR LOWERINGS)
        721158 AGENT
       1031315 AGENTS
       1461117 AGENT
                 (AGENT OR AGENTS)
L8           4 URIC ACID LOWERING AGENT
                 (URIC(W)ACID(W)LOWERING(W)AGENT)

=> s uric acid reducing agent
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       1469590 ACIDS
       4430938 ACID
                 (ACID OR ACIDS)
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             3 REDUCINGS
        319100 REDUCING
                 (REDUCING OR REDUCINGS)
        721158 AGENT
       1031315 AGENTS
       1461117 AGENT
                 (AGENT OR AGENTS)
L9           0 URIC ACID REDUCING AGENT
                 (URIC(W)ACID(W)REDUCING(W)AGENT)

=> d L8 1-4

L8   ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2005 ACS on STN
AN   2002:10270  CAPLUS
DN   136:64126
TI   Agent reducing uric acid levels for treatment of cardiovascular disease
     and hypertension
IN   Kivlighn, Salah; Johnson, Richard J.; Mazzali, Marilda
PA   Merck & Co., Inc., USA; University of Washington
SO   PCT Int. Appl., 49 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND  DATE        APPLICATION NO.          DATE
     ----------          ----  --------    -----------------------  --------
PI   WO 2002000210       A2    20020103    WO 2001-US20457          20010628
     WO 2002000210       A3    20021024
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM,
             HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT,
             LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
             SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
             YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
             BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     CA 2413201          AA    20020103    CA 2001-2413201          20010628
     US 2002019360       A1    20020214    US 2001-892505           20010628
     EP 1317258          A2    20030611    EP 2001-946722           20010628
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
     JP 2004517804       T2    20040617    JP 2002-504992           20010628
PRAI US 2000-214825P     P     20000628
     WO 2001-US20457     W     20010628
```

L8 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:379871 CAPLUS
DN 135:147004
TI A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis
AU Goldman, Stanton C.; Holcenberg, John S.; Finklestein, Jerry Z.; Hutchinson, Raymond; Kreissman, Susan; Johnson, F. Leonard, Tou, Conrad, Harvey, Elizabeth; Morris, Erin; Cairo, Mitchell S.
CS Department of Pediatric Hematology/Oncology, North Texas Hospital for Children at Medical City, Dallas, TX, USA
SO Blood (2001), 97(10), 2998-3003
CODEN: BLOOAW; ISSN: 0006-4971
PB American Society of Hematology
DT Journal
LA English
RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:569285 CAPLUS
DN 129:301145
TI Decreased serum concentrations of 1,25(OH)2-vitamin D3 in patients with gout
AU Takahashi, Sumio; Yamamoto, Tetsuya; Moriwaki, Yuji; Tsutsumi, Zenta; Yamakita, Jun-ichi; Higashino, Kazuya
CS Third Department Internal Medicine, Hyogo College Medicine, Nishinomiya, Hyogo, 663, Japan
SO Advances in Experimental Medicine and Biology (1998), 431(Purine and Pyrimidine Metabolism in Man IX, 1998), 57-60
CODEN: AEMBAP; ISSN: 0065-2598
PB Plenum Publishing Corp.
DT Journal
LA English
RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1992:221600 CAPLUS
DN 116:221600
TI Serum uric acid-lowering agents containing 4-(heteroarylamino)phenols
IN Shibata, Hisao; Kubo, Hideji; Matsuno, Taro; Kamisako, Takuji
PA Otsuka Pharmaceutical Factory, Inc., Japan
SO Jpn. Kokai Tokkyo Koho, 8 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 04018021	A2	19920122	JP 1990-301610	19901106
PRAI	JP 1989-292894	A1	19891109		

OS MARPAT 116:221600

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Connection closed by remote host

L1 ANSWER 1 OF 5 EPFULL COPYRIGHT 2005 EPO/FIZ KA on STN

ACCESSION NUMBER: 2001:70498 EPFULL
DATA UPDATE DATE: 20040602
DATA UPDATE WEEK: 200423
TITLE (ENGLISH): USE OF AGENTS CAPABLE OF REDUCING URIC ACID LEVELS FOR THE TREATMENT OF CARDIOVASCULAR DISEASE
TITLE (FRENCH): UTILISATION D'AGENTS CAPABLES DE REDUIRE LE TAUX D'ACIDE URIQUE DANS LE TRAITEMENT DE MALADIE CARDIOVASCULAIRE
TITLE (GERMAN): VERWENDUNG VON MITTELN ZUR VERMINDERUNG DES HARNSAeURESPIEGELS ZUR BEHANDLUNG VON KARDIOVASKULAeREN ERKRANKUNGEN
INVENTOR(S): **KIVLIGHN, Salah, 4765 Cheshire Road, Doylestown, PA 18901, US**; JOHNSON, Richard, J., 4603 Beech Street, Bellaire, TX 77410, US; MAZZALI, Marilda, Deptm.de Clinica Medica-FCM/UNICAMP, cAMPINAS-S.P. 13083-970, BZ
PATENT APPLICANT(S): Merck & Co., Inc., 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907, US; University of Washington, Technology Transfer Department, Suite 200, 1107 NE 45th Street, Box 354810, Seattle, WA 98105-4681, US
PATENT APPL. NUMBER: 2645180; 2243812
AGENT: Hill, Justin John, McDermott, Will & Emery, 7 Bishopsgate, London EC2N 3AR, GB
AGENT NUMBER: 127251
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
LANGUAGE OF PROCEDURE: English
LANGUAGE OF TITLE: German; English; French
DOCUMENT TYPE: Patent
PATENT INFO TYPE: EPA2 Application published without search report
PATENT INFORMATION:
PATENT INFORMATION:
PATENT INFORMATION:

NUMBER	KIND	DATE
NUMBER	KIND	DATE
NUMBER	KIND	DATE
EP 1317258	A2	20030611
EP 1317258	A3	20021024
WO 2002000210		20020103

DESIGNATED STATES: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR
APPLICATION INFO.: EP 2001-946722 A 20010628
WO 2001-US20457 A 20010628
PRIORITY INFO.: US 2000-214825P P 20000628

L1 ANSWER 2 OF 5 GBFULL COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER: 2281298 GBFULL ED 20041103
TITLE: Imidazo-pyridine angiotensin II receptor agonists
INVENTOR(S): **KIVLIGHN**, SALAH; ZINGARO, GLORIA J; LOTTI, VICTOR J; RIVERO, RALPH A; SIEGL, PETER K S
PATENT APPLICANT(S): MERCK & CO INC
US
DOCUMENT TYPE: Patent
PATENT INFO TYPE: GBA Application published
PATENT INFO:

NUMBER	KIND	DATE
GB 2281298	A	19950301

APPLICATION INFO.: GB 1994-16916 A 19940822
PRIORITY INFO.: US 1993-113874 A 19930830

L1 ANSWER 3 OF 5 PCTFULL COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER: 2002000210 PCTFULL ED 20020814

TITLE (ENGLISH): TREATMENT FOR CARDIOVASCULAR DISEASE
TITLE (FRENCH): TRAITEMENT DE MALADIE CARDIO-VASCULAIRE
INVENTOR(S): **KIVLIGHN, Salah;**
JOHNSON, Richard, J.;
MAZZALI, Marilda
PATENT ASSIGNEE(S): MERCK &CO., INC.;
UNIVERSITY OF WASHINGTON;
KIVLIGHN, Salah;
JOHNSON, Richard, J.;
MAZZALI, Marilda
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2002000210	A2	20020103

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR
CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL
IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK
MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM
TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD
SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY
DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ CF
CG CI CM GA GN GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2001-US20457 A 20010628
PRIORITY INFO.: 2000-60/214,825 20000628
US 2000-60/214,825 20000628

L1 ANSWER 4 OF 5 USPATFULL on STN
ACCESSION NUMBER: 2002:32538 USPATFULL
TITLE: Treatment for cardiovascular disease
INVENTOR(S): **Kivlighn, Saluh**, Doylestown, PA, UNITED STATES
Johnson, Richard, Bellaire, TX, UNITED STATES
Mazzali, Marilda, Houston, TX, UNITED STATES
PATENT ASSIGNEE(S): Merck & Co., Inc. (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002019360	A1	20020214	
APPLICATION INFO.:	US 2001-892505	A1	20010628	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2000-214825P	20000628	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: McDERMOTT, WILL & EMERY, 600 13th Street, N.W., Washington, DC, 20005-3096
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 12 Drawing Page(s)
LINE COUNT: 1402
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 5 OF 5 USPATFULL on STN
ACCESSION NUMBER: 95:75976 USPATFULL
TITLE: Pharmaceutical treatment methods using angiotensin II receptor agonists bearing a thiophene moiety
INVENTOR(S): **Kivlighn, Salah**, Blue Bell, PA, United States
Lotti, Victor J., Harleysville, PA, United States
Rivero, Ralph A., Tinton Falls, NJ, United States
Siegl, Peter K. S., Blue Bell, PA, United States
Zingaro, Gloria J., Harleysville, PA, United States
PATENT ASSIGNEE(S): Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE

PATENT INFORMATION:	US 5444067	19950822
APPLICATION INFO.:	US 1993-113874	19930830 (8)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	Granted	
PRIMARY EXAMINER:	Dentz, Bernard	
LEGAL REPRESENTATIVE:	Camara, Valerie J., Daniel, Mark R., DiPrima, Joseph F.	
NUMBER OF CLAIMS:	6	
EXEMPLARY CLAIM:	1	
LINE COUNT:	498	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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     (FILE 'HOME' ENTERED AT 15:07:25 ON 31 MAR 2005)

     FILE 'EPFULL, FRFULL, GBFULL, PATDPAFULL, PCTFULL, RDISCLOSURE,
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                E KIVLIGHN S/IN
L1              5 S E4-E5

     FILE 'CAPLUS' ENTERED AT 15:10:30 ON 31 MAR 2005
                E KIVLIGHN S/AU
L2             61 S E3-E7
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=> d ibib abs 1-11

L2 ANSWER 1 OF 61 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:408498 CAPLUS
DOCUMENT NUMBER: 139:147286
TITLE: Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease?
AUTHOR(S): Johnson, Richard J.; Kang, Duk-Hee; Feig, Daniel; **Kivlighn, Salah**; Kanellis, John; Watanabe, Susumu; Tuttle, Katherine R.; Rodriguez-Iturbe, Bernardo; Herrera-Acosta, Jaime; Mazzali, Marilda
CORPORATE SOURCE: Division of Nephrology and Texas Children's Hospital, Baylor College of Medicine, Houston, TX, USA
SOURCE: Hypertension (2003), 41(6), 1183-1190
CODEN: HPRTDN; ISSN: 0194-911X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Hyperuricemia is associated with hypertension, vascular disease, renal disease, and cardiovascular events. In this report, we review the epidemiol. evidence and potential mechanisms for this association We also summarize exptl. studies that demonstrate that uric acid is not inert but may have both beneficial functions (acting as an antioxidant) as well as detrimental actions (to stimulate vascular smooth muscle cell proliferation and induce endothelial dysfunction). A recently developed exptl. model of mild hyperuricemia also provides the first provocative evidence that uric acid may have a pathogenic role in the development of hypertension, vascular disease, and renal disease. Thus, it is time to reevaluate the role of uric acid as a risk factor for cardiovascular disease and hypertension and to design human studies to address this controversy.
REFERENCE COUNT: 104 THERE ARE 104 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 2 OF 61 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:787752 CAPLUS
DOCUMENT NUMBER: 138:37124
TITLE: Effects of aging and AT-1 receptor blockade on NO synthase expression and renal function in SHR
AUTHOR(S): Vaziri, N. D.; Wang, X. Q.; Ni, Z.; **Kivlighn, S.**; Shahinfar, S.
CORPORATE SOURCE: UCI Medical Center, Department of Medicine, Division of Nephrology and Hypertension, University of Irvine, Orange, CA, 92868, USA
SOURCE: Biochimica et Biophysica Acta (2002), 1592(2), 153-161
CODEN: BBACAQ; ISSN: 0006-3002
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In an earlier study, the authors found increased NO production and NO synthase (NOS) expression in renal and vascular tissues of prehypertensive and adult spontaneously hypertensive rats (SHR). This study was designed to determine the effects of aging and AT-1 receptor blockade (losartan 30 mg/kg/day beginning at 8 wk of age) on NO system in this model. Compared to the Wistar Kyoto (WKY) control rats, untreated SHR showed severe hypertension, elevated urinary NO metabolite (NO_χ) excretion, marked upregulations of renal and vascular eNOS and iNOS proteins, normal renal function and heart weight at 9 wk of age. Hypertension control with either AT-1 receptor or calcium channel blockade (felodipine 5 mg/kg/day) mitigated upregulation of NOS isoforms in the young SHR. With advanced age (63 wk), the untreated SHR showed increased proteinuria, renal insufficiency, cardiomegaly, reduced urinary NO_χ excretion and depressed renal and vascular NOS protein expressions as compared to the corresponding WKY group. AT-1 receptor blockade prevented proteinuria, renal insufficiency, cardiomegaly, and renal and vascular NOS deficiency. Thus, in young SHR, hypertension results in compensatory upregulation of renal and vascular NOS, which can be attenuated by vigorous

antihypertensive therapy. With advanced age, untreated SHR exhibit cardiomegaly, renal dysfunction and marked redns. of eNOS and iNOS compared with the aged WKY rats. Hypertension control with AT-1 receptor blockade initiated early in the course of the disease prevents target organ damage and preserves renal and vascular NOS.
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 3 OF 61 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:224618 CAPLUS
TITLE: From mechanisms and targets to risk assessment and treatment of cardiovascular and renal diseases
AUTHOR(S): Brooks, David P.; **Kivlighn, Salah D.**
CORPORATE SOURCE: GlaxoSmithKline, King of Prussia, PA, 19406-0939, USA
SOURCE: Current Opinion in Pharmacology (2002), 2(2), 119-120
CODEN: COPUBK; ISSN: 1471-4892
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; Editorial
LANGUAGE: English
AB Unavailable

L2 ANSWER 4 OF 61 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:212269 CAPLUS
DOCUMENT NUMBER: 137:150191
TITLE: Cardiovascular and Renal. [In: Curr. Opin. Pharmacol., 2002; 2(2)]
AUTHOR(S): Brooks, David P.; **Kivlighn, Salah D.**; Editors
CORPORATE SOURCE: UK
SOURCE: (2002) Publisher: (Elsevier Science Ltd.: Oxford, UK), 89 pp.
DOCUMENT TYPE: Book
LANGUAGE: English
AB Unavailable

L2 ANSWER 5 OF 61 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:10270 CAPLUS
DOCUMENT NUMBER: 136:64126
TITLE: Agent reducing uric acid levels for treatment of cardiovascular disease and hypertension
INVENTOR(S): **Kivlighn, Salah**; Johnson, Richard J.; Mazzali, Marilda
PATENT ASSIGNEE(S): Merck & Co., Inc., USA; University of Washington
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002000210	A2	20020103	WO 2001-US20457	20010628
WO 2002000210	A3	20021024		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2413201	AA	20020103	CA 2001-2413201	20010628
US 2002019360	A1	20020214	US 2001-892505	20010628
EP 1317258	A2	20030611	EP 2001-946722	20010628
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

JP 2004517804 T2 20040617 JP 2002-504992 20010628
PRIORITY APPLN. INFO.: US 2000-214825P P 20000628
WO 2001-US20457 W 20010628

AB This invention relates to a method for treating and preventing hypertension by administering a therapeutically effective amount of an agent capable of reducing uric acid levels in a patient in need of such treatment. Addnl., the scope of the invention includes a method of treating coronary heart disease by administering a therapeutically effective amount of an agent capable of reducing uric acid levels in a patient in need of such treatment. Allopurinol administered from the initiation of an oxonic acid diet prevented the development of hyperuricemia and hypertension. In hypertensive, hyperuricemic rats, either withdrawal of the oxonic acid or adding allopurinol also resulted in a reduction in the blood pressure in association with a fall in serum uric acid values.

L2 ANSWER 6 OF 61 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:887836 CAPLUS
DOCUMENT NUMBER: 136:148867
TITLE: Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism
AUTHOR(S): Mazzali, Marilda; Hughes, Jeremy; Kim, Yoon-Goo; Jefferson, J. Ashley; Kang, Duk-Hee; Gordon, Katherine L.; Lan, Hui Y.; **Kivlighn, Salah**; Johnson, Richard J.
CORPORATE SOURCE: Division of Nephrology, University of Washington Medical Center, Seattle, WA, USA
SOURCE: Hypertension (2001), 38(5), 1101-1106
CODEN: HPRTDN; ISSN: 0194-911X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB An elevation in circulating serum uric acid is strongly associated with the development of hypertension and renal disease, but whether uric acid has a causal role or whether it simply indicates patients at risk for these complications remains controversial. We tested the hypothesis that uric acid may have a causal role in the development of hypertension and renal disease by examining the effects of mild hyperuricemia in rats. Mild hyperuricemia was induced in rats by providing a uricase inhibitor (oxonic acid) in the diet. Hyperuricemic rats developed elevated blood pressure after 3 wk, whereas control rats remained normotensive. The development of hypertension was prevented by concurrent treatment with either a xanthine oxidase inhibitor (allopurinol) or a uricosuric agent (benziodarone), both of which lowered uric acid levels. Blood pressure could also be lowered by reducing uric acid levels with either allopurinol or oxonic acid withdrawal. A direct relationship was found between blood pressure and uric acid ($r=0.75$, $n=69$), with a 10-mm Hg blood pressure increase for each 0.03-mmol/L (0.5-mg/dL) incremental rise in serum uric acid. The kidneys were devoid of urate crystals and were normal by light microscopy. However, immunohistochem. stains documented an ischemic type of injury with collagen deposition, macrophage infiltration, and an increase in tubular expression of osteopontin. Hyperuricemic rats also exhibited an increase in juxtaglomerular renin and a decrease in macula densa neuronal NO synthase. Both the renal injury and hypertension were reduced by treatment with enalapril or L-arginine. In conclusion, mild hyperuricemia causes hypertension and renal injury in the rat via a crystal-independent mechanism, with stimulation of the renin-angiotensin system and inhibition of neuronal NO synthase.

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 7 OF 61 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:387247 CAPLUS
DOCUMENT NUMBER: 136:128770
TITLE: Hyperuricemia exacerbates chronic cyclosporine nephropathy
AUTHOR(S): Mazzali, Marilda; Kim, Yoon-Goo; Suga, Shin-Ichi; Gordon, Katherine L.; Kang, Duk-Hee; Jefferson, J.

Ashley; Hughes, Jeremy; **Kivlighn, Salah D.**; Lan, Hui Y.; Johnson, Richard J.
CORPORATE SOURCE: Division of Nephrology, University of Washington Medical Center, Seattle, WA, 98185, USA
SOURCE: Transplantation (2001), 71(7), 900-905
CODEN: TRPLAU; ISSN: 0041-1337
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Background. Hyperuricemia frequently complicates cyclosporine (CSA) therapy. The observation that longstanding hyperuricemia is associated with chronic tubulointerstitial disease and intrarenal vasoconstriction raised the hypothesis that hyperuricemia might contribute to chronic CSA nephropathy. Methods. CSA nephropathy was induced by the administration of CSA (15 mg/kg/day) for 5 and 7 wk to rats on a low salt diet (CSA group). The effect of hyperuricemia on CSA nephropathy was determined by blocking the hepatic enzyme uricase with oxonic acid (CSA-OA). Control groups included rats treated with vehicle (VEH) and oxonic acid alone (OA). Histol. and functional studies were determined at sacrifice. Results. CSA-treated rats developed mild hyperuricemia with arteriolar hyalinosis, tubular injury, and striped interstitial fibrosis. CSA-OA-treated rats had higher uric acid levels in association with more severe arteriolar hyalinosis and tubulointerstitial damage. Intrarenal urate crystal deposition was absent in all the groups. Both CSA- and CSA-OA-treated rats had increased renin and decreased NOS1 and NOS3 in their kidneys, and these changes are more evident in CSA-OA-treated rats. Conclusion. An increase in uric acid exacerbates CSA nephropathy in the rat. The mechanism does not involve intrarenal uric acid crystal deposition and appears to involve the activation of the renin angiotensin system and inhibition of intrarenal nitric oxide production
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 8 OF 61 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:821359 CAPLUS
DOCUMENT NUMBER: 134:251047
TITLE: Involvement of macrophage migration inhibitory factor (MIF) in experimental uric acid nephropathy
AUTHOR(S): Kim, Yoon-Goo; Huang, Xiao-Ru; Suga, Shin-ichi; Mazzali, Marilda; Tang, Dongjiang; Metz, Christine; Bucala, Richard; **Kivlighn, Salah**; Johnson, Richard J.; Lan, Hui Y.
CORPORATE SOURCE: Division of Nephrology, University of Washington Medical Center, Seattle, WA, USA
SOURCE: Molecular Medicine (New York) (2000), 6(10), 837-848
CODEN: MOMEF3; ISSN: 1076-1551
PUBLISHER: Johns Hopkins University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Deposition of uric acid in the kidney can lead to progressive tubulointerstitial injury with granuloma formation. The authors hypothesized that uric acid crystal deposition may induce granuloma formation by stimulating local expression of macrophage migration inhibitory factor (MIF), which is a known mediator of delayed type hypersensitivity (DTH). A model of acute uric acid nephropathy was induced in rats by the administration of oxonic acid (an inhibitor of uricase), together with uric acid supplements. MIF expression and local cellular response were examined by in situ hybridization and immunohistochem. Kidney tissue examined at 35 days post-treatment showed widespread tubulointerstitial damage with intratubular uric acid crystal deposition and granuloma formation. Tubules within the areas of granuloma showed a six-fold increase in MIF mRNA, compared with uninvolved areas by in situ hybridization. Moreover, the areas of increased MIF mRNA expression correlated with sites of dense accumulation of macrophages and T cells, and these cells were activated when assessed by the expression of interleukin-2R (IL-2R) and (MHC) class II. Interestingly, cytoplasmic staining for MIF protein in the uric acid (UA) crystal-associated granulomatous lesions was reduced, indicating a rapid MIF secretion by

damaged tubules and macrophages secondary to uric acid crystal stimulation. This was confirmed by the demonstration of a marked increase in urinary MIF protein by Western blot anal. Control rats fed either a normal diet or only oxonic acid had no discernible evidence of renal disease by routine light microscopy and minimal tubular expression of MIF mRNA and protein. These data suggest that intrarenal granulomas in urate nephropathy may be the consequence of a crystal induced DTH reaction mediated by MIF.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 9 OF 61 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:288244 CAPLUS

DOCUMENT NUMBER: 133:187825

TITLE: Inhibition of early atherogenesis by losartan in monkeys with diet-induced hypercholesterolemia

AUTHOR(S): Strawn, William B.; Chappell, Mark C.; Dean, Richard H.; **Kivlighn, Salah**; Ferrario, Carlos M.

CORPORATE SOURCE: Wake Forest University School of Medicine, Winston-Salem, NC, 27157, USA

SOURCE: Circulation (2000), 101(13), 1586-1593
CODEN: CIRCAZ; ISSN: 0009-7322

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Angiotensin II may contribute to atherogenesis by facilitating the proliferative and inflammatory response to hypercholesterolemia. This study determined, in a primate model of diet-induced atherosclerosis, the effect of AT1 blockade on fatty-streak formation, plasma lipids, and surrogate markers of vascular injury. Male cynomolgus monkeys fed a diet containing 0.067 mg cholesterol/kJ for 20 wk were given losartan (180 mg/d, n=6) or vehicle (n=8) for 6 wk starting at week 12 of the dietary regimen. Arterial pressure, heart rate, plasma total and lipoprotein cholesterol concns., and lipoprotein particle sizes and subclass distributions were unaffected by treatment. Losartan caused significant ($P<0.05$) increases in plasma angiotensin II and angiotensin-(1-7). Compared with vehicle-treated controls, losartan reduced the extent of fatty streak in the aorta, the coronary arteries, and the carotid arteries by ≈50% ($P<0.05$). A significant ($P<0.05$) reduction in the susceptibility of LDL to in vitro oxidation, serum levels of monocyte chemoattractant protein-1, and circulating monocyte CD11b expression were also associated with losartan treatment. In addition, serum levels of vascular cell adhesion mol.-1 and E-selectin did not change during treatment but increased after discontinuation of losartan. Serum C-reactive protein, platelet aggregability, and white cell counts were not modified by losartan. Conclusions-This study demonstrates for the first time an antiatherogenic effect of AT1 receptor blockade in nonhuman primates. Losartan inhibited fatty-streak formation through mechanisms that may include protection of LDL from oxidation and suppression of vascular monocyte activation and recruitment factors.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 10 OF 61 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:335406 CAPLUS

DOCUMENT NUMBER: 131:125183

TITLE: Pharmacological properties of J-104132 (L-753,037), a potent, orally active, mixed ETA/ETB endothelin receptor antagonist

AUTHOR(S): Nishikibe, M.; Ohta, H.; Okada, M.; Ishikawa, K.; Hayama, T.; Fukuroda, T.; Noguchi, K.; Saito, M.; Kanoh, T.; Ozaki, S.; Kamei, T.; Hara, K.; William, D.; **Kivlighn, S.**; Krause, S.; Gabel, R.; Zingaro, G.; Nolan, N.; O'Brien, J.; Clayton, F.; Lynch, J.; Pettibone, D.; Siegl, P.

CORPORATE SOURCE: Tsukuba Research Institutes and Development Research Laboratories, Banyu Pharmaceutical Co., Ltd., Ibaraki, Japan

SOURCE: Journal of Pharmacology and Experimental Therapeutics (1999), 289(3), 1262-1270
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB J-104132 [(+)-(5S,6R,7R)-2-butyl-7-[2-((2S)-2-carboxypropyl)-4-methoxyphenyl]-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine-6-carboxylic acid; also referred to as L-753,037] is a potent, selective inhibitor of ETA and ETB endothelin (ET) receptors (e.g., Ki: cloned human ETA = 0.034 nM; cloned human ETB = 0.104 nM). In both ligand-binding and isolated tissue preparation protocols, the inhibition of ET receptors with J-104132 is reversible and competitive. In vitro, J-104132 is a potent antagonist of ET-1-induced accumulation of [3H]inositol phosphates in Chinese hamster ovary cells stably expressing cloned human ETA receptors (IC50 = 0.059 nM), ET-1-induced contractions in rabbit iliac artery (pA2 = 9.70) and of BQ-3020-induced contractions in pulmonary artery (pA2 = 10.14). J-104132 is selective for ET receptors because it had no effect on contractions elicited by norepinephrine or KCl in the vascular prepns. The in vivo potency of J-104132 was assessed using challenges with exogenous ET-1. In conscious mice, 5 nmol/kg i.v. ET-1 causes death. Pretreatment with J-104132 prevents the lethal response to ET-1 when administered i.v. (ED50 = 0.045 mg/kg) or p.o. in fed animals (ED50 = 0.35 mg/kg). In conscious, normotensive rats, pressor responses to 0.5 nmol/kg i.v. ET-1 are inhibited by J-104132 after i.v. (0.1 mg/kg) or p.o. (1 mg/kg) administration. In anesthetized dogs, ET-1 was administered directly into the renal artery or brachial artery to generate dose-response (blood flow) curves, and the inhibitory potency of J-104132 (i.v. infusion) was quantified. J-104132 produced greater than 10-fold shifts in the ET-1 dose-response curves at 0.03 mg/kg/h (renal) and 0.3 mg/kg/h (branchial). Oral bio-availability of J-104132 in rats was approx. 40%. These studies indicate that J-104132 is a selective, potent, orally active antagonist of both ETA and ETB receptors and is an excellent pharmacol. tool to explore the therapeutic use of a mixed ETA/ETB receptor antagonist.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 11 OF 61 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:448225 CAPLUS
DOCUMENT NUMBER: 129:215079
TITLE: Role of endothelin and nitric oxide imbalance in the pathogenesis of hypoxia-induced arterial hypertension
AUTHOR(S): Ni, Zhenmin; Bemanian, Shahrooz; **Kivlighn, Salah D.**; Vaziri, Nosratola D.
CORPORATE SOURCE: Division of Nephrology, Department of Medicine, University of California, Irvine, Irvine, CA, USA
SOURCE: Kidney International (1998), 54(1), 188-192
CODEN: KDYIA5; ISSN: 0085-2538
PUBLISHER: Blackwell Science, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have recently demonstrated that prolonged hypobaric hypoxia can lead to a hematocrit-independent sustained arterial hypertension (HTN) in genetically normotensive Sprague-Dawley rats. The rise in blood pressure in the hypoxic animals was accompanied by a marked but transient increase in plasma endothelin level. In addition, hypoxia has been shown to decrease nitric oxide (NO) production by cultured endothelial cells. This study was designed to test the hypothesis that hypoxia-induced HTN may be mediated by increased endothelin and/or decreased NO production Blood pressure, plasma endothelin and urinary NO metabolites (NOx) were monitored in rats during a 24-day exposure to hypobaric hypoxia (air pressure = 390 mm Hg). The results were compared with those obtained in animals maintained under normoxic condition (control group). To test the possible role of excess endothelin and depressed NO production, the studies were repeated using subgroups of animals treated with either an endothelin receptor ET-A/B blocker (L-754142) or L-arginine. The untreated hypoxic group exhibited a

threefold rise in plasma endothelin and a threefold fall in urinary NOx, prior to the onset of HTN. Endothelin receptor blockade led to a further fall in urinary NOx excretion and failed to mitigate HTN. In contrast, L-arginine supplementation improved the urinary NOx excretion and prevented HTN. Neither therapy affected the hypoxia-induced erythrocytosis. We conclude that hypoxia-induced HTN is associated with depressed NO production and can be mitigated by L-arginine supplementation.

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT